

## INTISARI

**Latar Belakang:** Cedera iskemia/reperfusi (I/R) pada ginjal merupakan penyebab sekunder terjadinya glomerulosklerosis yang dapat mempercepat progresi gagal ginjal akut menjadi kronis. Terapi regeneratif menggunakan eksosom menjadi terapi alternatif yang menjanjikan karena memiliki efek anti-inflamasi, anti-apoptosis, dan anti-fibrotik. Salah satunya eksosom *human-Wharton's Jelly-derived Mesenchymal Stem Cell* (hWJ-MSCs) yang diketahui memiliki potensi dalam menurunkan progresivitas akibat cedera I/R ginjal.

**Tujuan Penelitian:** Mengkaji efek pemberian eksosom hWJ-MSCs terhadap faktor glomerulosklerosis pada gagal ginjal dengan model cedera I/R ginjal periode kronis.

**Metode:** Tikus Wistar jantan, berusia 10 minggu, sejumlah 26 ekor dibagi menjadi 5 kelompok; SO (*sham-operated*, n=6), IR (cedera I/R, n=5), IR+E1 (cedera I/R+dosis rendah, n=5), IR+E2 (cedera I/R+dosis sedang, n=5), dan IR+E3 (cedera I/R+dosis tinggi, n=5). Eksosom diberikan secara intravena 1 hari setelah cedera I/R dibuat. Terminasi hewan dilakukan 21 hari setelah model terbentuk. Pemeriksaan total albuminuria dan skor proteinuria dilakukan menggunakan urin tampung 24 jam. Pewarnaan PAS dilakukan untuk menilai skor glomerulosklerosis. IHK Podocin dilakukan untuk melihat persebaran Podocin pada glomerulus ginjal. Pemeriksaan ekspresi mRNA  $\beta$ -catenin, E-cadherin, Nephtrin, dan Vimentin dilakukan dengan metode RT-PCR dan housekeeping gene  $\beta$ -aktin. Analisis statistik dilakukan menggunakan one-way ANOVA; post-hoc LSD, dan Kruskal-Wallis; post-hoc Dunn's test.

**Hasil Penelitian:** Hasil penelitian menunjukkan pemeriksaan total albuminuria, skor proteinuria, skor glomerulosklerosis dan ekspresi mRNA  $\beta$ -catenin lebih rendah signifikan pada kelompok yang menerima eksosom dosis tinggi dibandingkan kelompok IR ( $p=0,009$ ;  $p=0,002$ ;  $p=0,030$ ;  $p=0,011$ ). Sementara ekspresi mRNA E-cadherin lebih tinggi signifikan pada ketiga kelompok dosis eksosom dibandingkan kelompok IR ( $p=0,011$ ;  $p=0,015$ ,  $p=0,001$ ), begitu juga dengan ekspresi mRNA Nephtrin ( $p=0,00$ ;  $p=0,00$ ;  $p=0,00$ ). Sedangkan ekspresi mRNA Vimentin tidak menunjukkan adanya perbedaan signifikan antar kelompok.

**Kesimpulan:** Pemberian eksosom hWJ-MSCs dosis tinggi mampu memperbaiki fungsi ginjal dan glomerulosklerosis melalui penghambatan cedera podosit akibat cedera I/R pada ginjal tikus.

**Kata Kunci:** Eksosom hWJ-MSCs, cedera iskemia/reperfusi, total albuminuria, proteinuria, glomeruloskelrosis,  $\beta$ -catenin, E-cadherin, Nephtrin, Vimentin, IHK Podocin.

## ABSTRACT

**Background:** Renal ischemia/reperfusion (I/R) injury is a secondary cause of glomerulosclerosis that accelerates the progression from acute kidney injury to chronic kidney disease. Regenerative therapy using exosomes has emerged as a promising alternative because of their anti-inflammatory, anti-apoptotic, and anti-fibrotic. Exosomes derived from human Wharton's Jelly–Mesenchymal Stem Cells (hWJ-MSCs) have shown potential in attenuating the progression of renal damage following I/R injury.

**Objective:** To analyze the effect of hWJ-MSC-derived exosomes on glomerulosclerosis in a chronic phase renal I/R injury model.

**Methods:** Twenty-six male Wistar rats (10 weeks old) were divided into five groups: SO (sham-operated, n=6), IR (renal ischemia–reperfusion [I/R] injury, n=5), IR+E1 (I/R+low-dose, n=5), IR+E2 (I/R+medium-dose, n=5), and IR+E3 (I/R+high-dose, n=5). Exosomes were administered intravenously one day after surgery I/R. Animals were sacrificed 21 days after model induction. Total albuminuria and proteinuria score were measured from 24-hour urine collections. PAS staining was performed to assess glomerulosclerosis. Podocin distribution within the glomeruli was evaluated by immunohistochemistry. Renal mRNA expression of  $\beta$ -catenin, E-cadherin, Nephtrin, and Vimentin was analyzed using RT-PCR, with  $\beta$ -actin as the housekeeping gene. Statistical analyses were conducted using one-way ANOVA; LSD post-hoc or Kruskal–Wallis tests; Dunn's post hoc tests, respectively.

**Results:** The results showed that total albuminuria, proteinuria score, glomerulosclerosis score, and  $\beta$ -catenin mRNA expression were significantly lower in the high-dose exosome group compared with the IR group ( $p = 0.009$ ;  $p = 0.002$ ;  $p = 0.030$ ;  $p = 0.011$ ). In contrast, E-cadherin mRNA expression was significantly higher in all three exosome dose groups compared with the IR group ( $p = 0.011$ ;  $p = 0.015$ ;  $p = 0.001$ , respectively), accompanied by significantly increased Nephtrin expression in all three exosome groups compared with the IR group. Meanwhile, Vimentin mRNA expression did not show any significant differences among the groups ( $p=0.617$ ).

**Conclusion:** Administration of high-dose hWJ-MSC-derived exosomes improved renal function and attenuated glomerulosclerosis by inhibiting podocyte injury following renal ischemia/reperfusion (I/R) in rats.

**Keywords:** hWJ-MSC exosomes, ischemia/reperfusion injury, total albuminuria, proteinuria, glomerulosclerosis,  $\beta$ -catenin, E-cadherin, Nephtrin, Vimentin, Podocin IHC.